Neuroscience II Pathology-lab

Dr. Bushra Al-Tarawneh, MD

Anatomical pathology
Mutah University
School of Medicine-

Department of Microbiology & Pathology
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Demyelinating diseases of CNS

Diseases of myelin are separated to two groups:

I. Demyelinating diseases

+acquired conditions. Damage to previously normal myelin.

+causes:

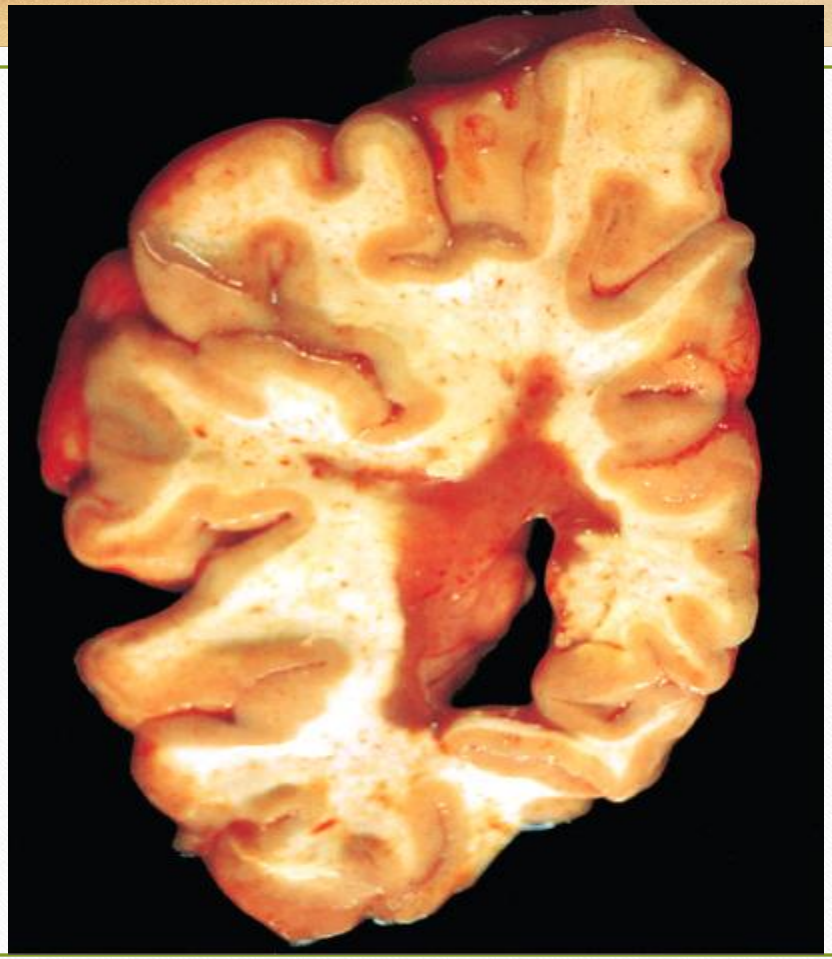
(1)immune mediated.

(2)oligodendrocytes viral infection (progressive multifocal Leukoencephalopathy → JC virus, a polyomavirus).

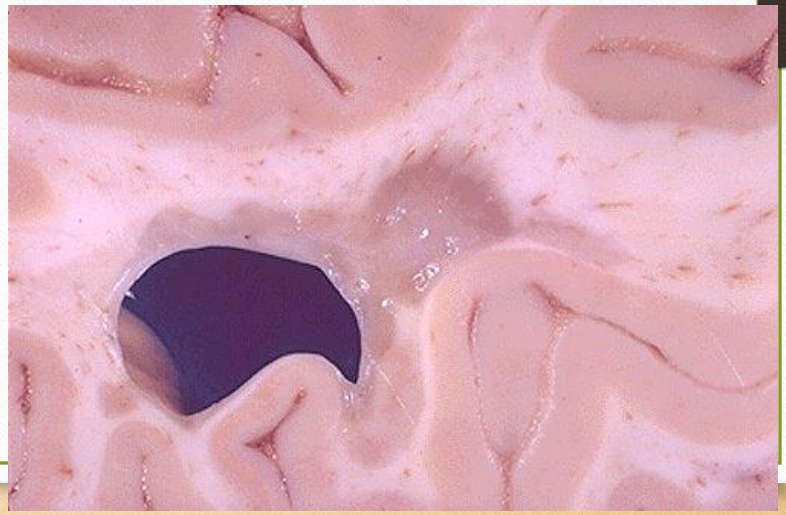
(3) injury caused by drugs or other toxic agents.

Multiple Sclerosis (MS)

- The most common demyelinating disease.
- An autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits that are separated in time and are attributable to patchy white matter lesions that are separated in space.
- M:F 1:2, rare in childhood & after the age of 50.
- The lesions of are caused by an autoimmune response directed against components of the myelin sheath.
- The clinical course takes the form of relapsing and remitting episodes of variable duration (weeks to months to years) marked by neurologic defects, followed by gradual and partial recovery of neurologic function.

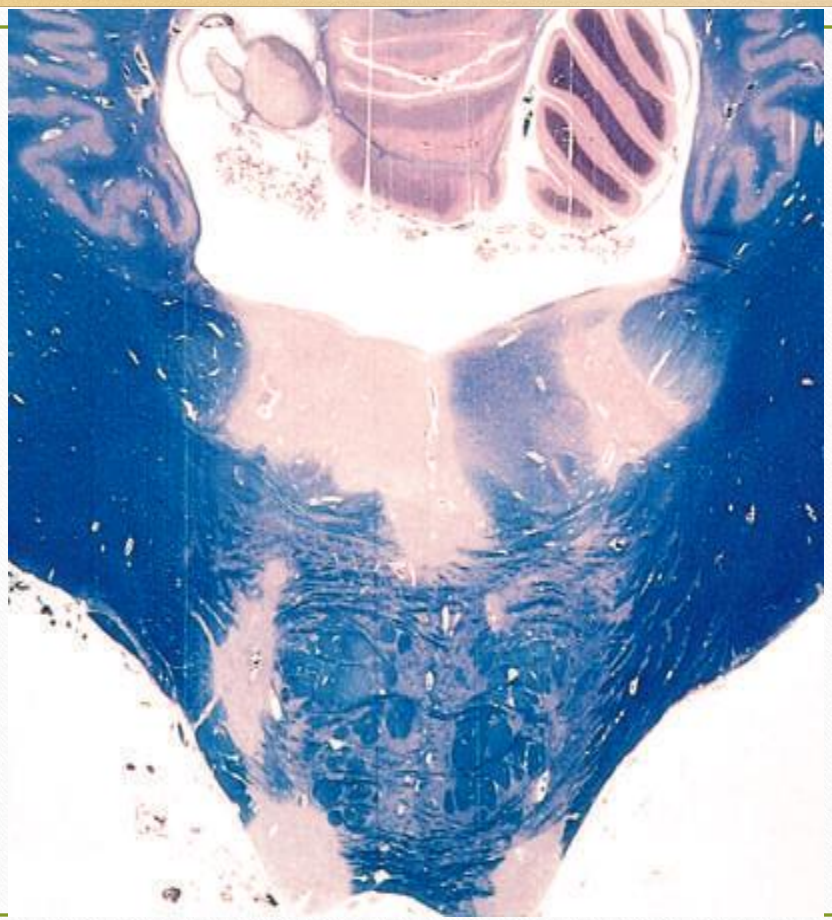


A white matter disease. Lesions → **plaques**: **discrete**, slightly depressed, glassy-appearing, and gray in color, and commonly near the ventricles.



Microscopically:
The active plaque, there is ongoing myelin breakdown associated with abundant foamy macrophages; lymphocytes are also present, mostly as perivascular cuffs, especially at the outer edge of the lesion. Active lesions are often centered on small veins; myelin is usually completely absent. but axons are relatively preserved.

In time, astrocytes undergo reactive changes. As lesions become quiescent, the inflammatory cells slowly disappear. Within inactive plaques, there is no macrophage-rich infiltrate, little to no myelin is found, and there is a reduction in the number of oligodendrocyte nuclei; instead, reactive gliosis is prominent. Axons in old gliotic plaques are usually greatly diminished in number



lesions are sharply defined microscopically:

+ **Active plaques** (ongoing myelin breakdown): contain abundant macrophages stuffed with myelin debris (lipid), also perivascular cuffs of Lymphocytes.

+**Inactive plaques** (quiescent): inflammation mostly disappears, leaving little to no myelin, & gliosis.

NEURODEGENERATIVE DISEASES

- Neurodegenerative diseases are disorders characterized by the progressive loss of particular groups of neurons, which often have shared functions.

- The pathologic process that is common across most of the neurodegenerative diseases is the accumulation of protein aggregates (hence the occasional use of the term “proteinopathy”).

Alzheimer Disease (AD)

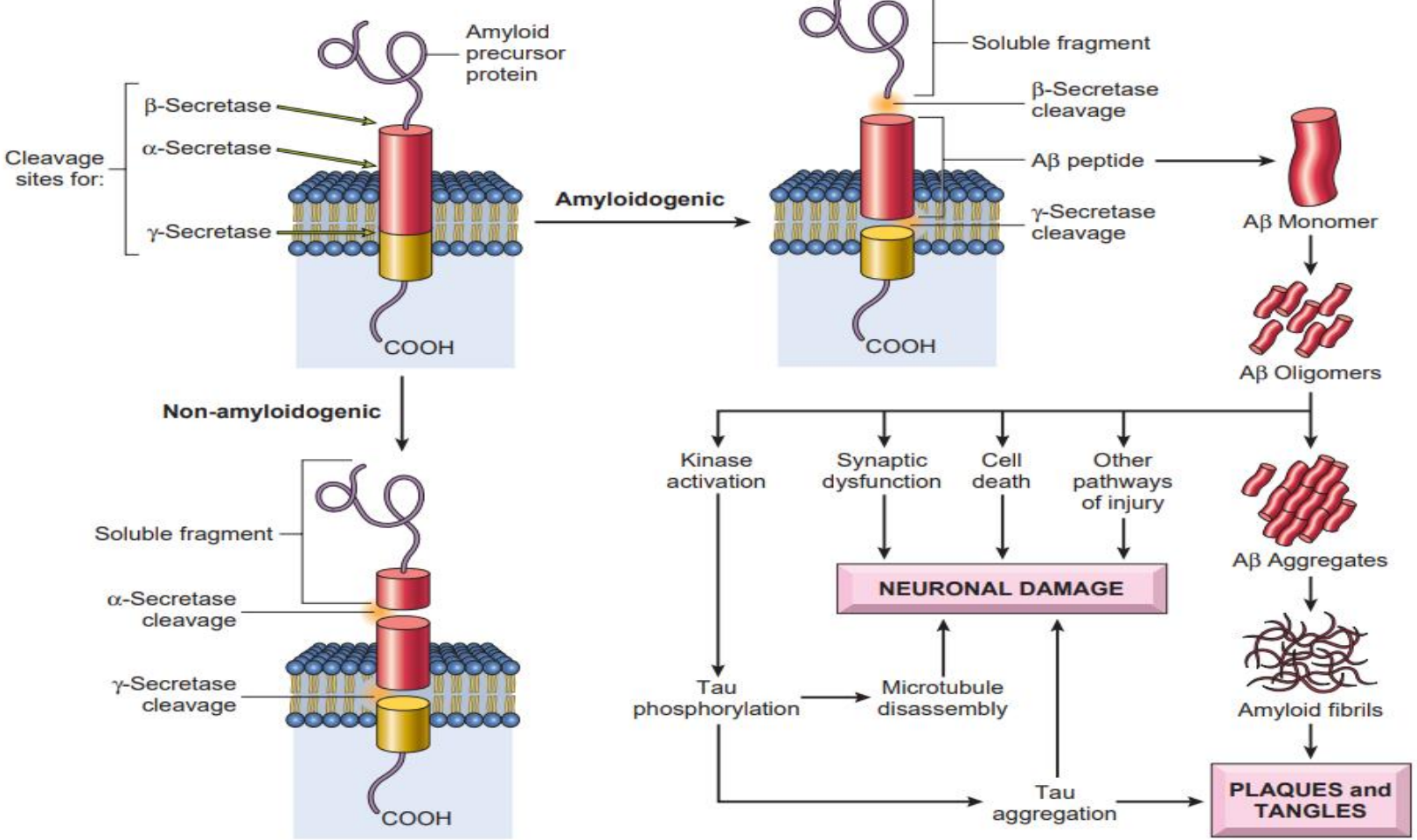


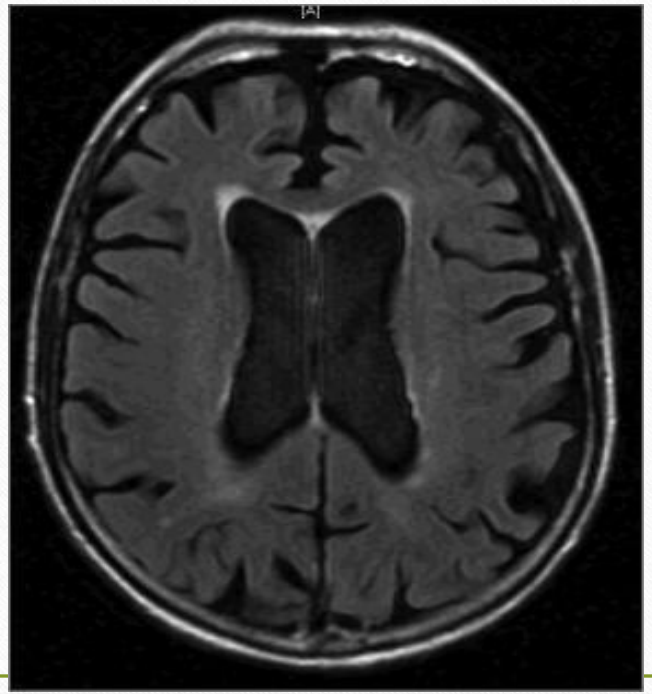
Figure 28.35 Protein aggregation in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

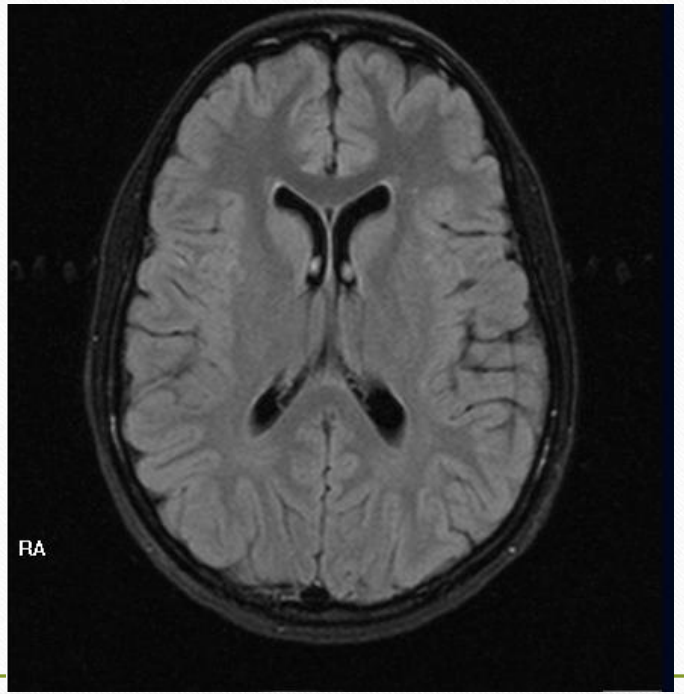
AD – Pathogenesis

- **Aβ generation is the critical initiating event to develop AD,** it's derived from a membrane protein → amyloid precursor protein (APP).
- APP processed in 2 ways pathways:
  (1) Starts with α-secretase (non-amyloidogenic), **no Aβ generation.**
  (2) Starts with β-secretase (amyloidoigenic), **Aβ generation.**
- APP gene located on chr. 21 (~Down syndrome).
- Aβ is highly prone to aggregation and causing neural dysfunction, & elicits a local inflammatory response that can result in further cell injury.

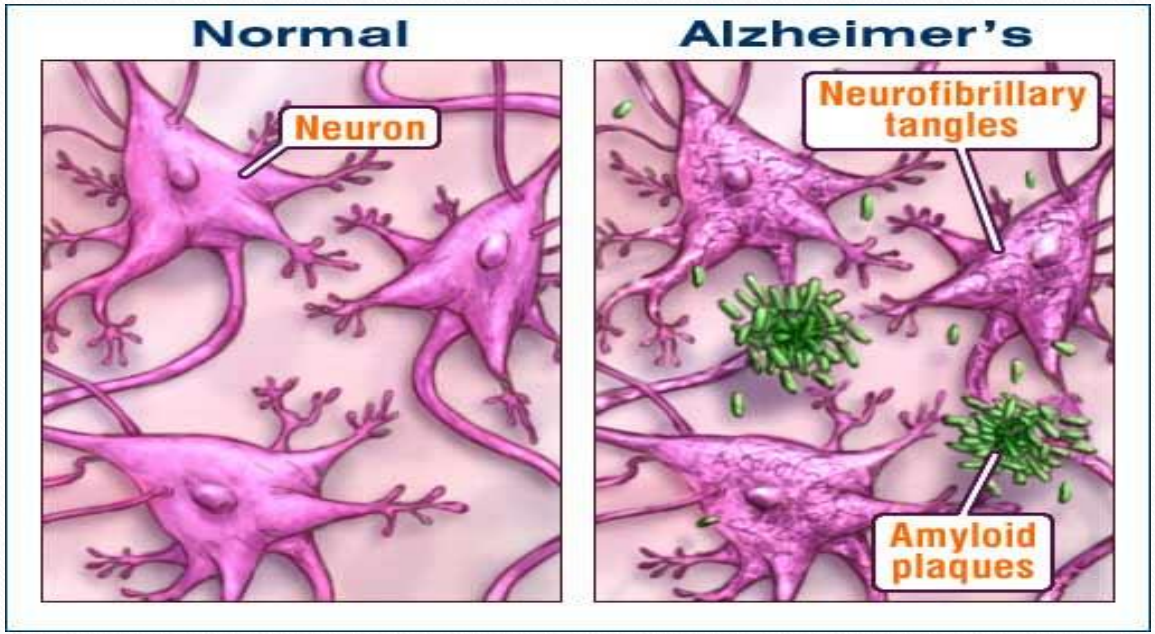
A variable degree of cortical atrophy, resulting in a widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.

The atrophy produces a compensatory ventricular enlargement (hydrocephalus ex vacuo)

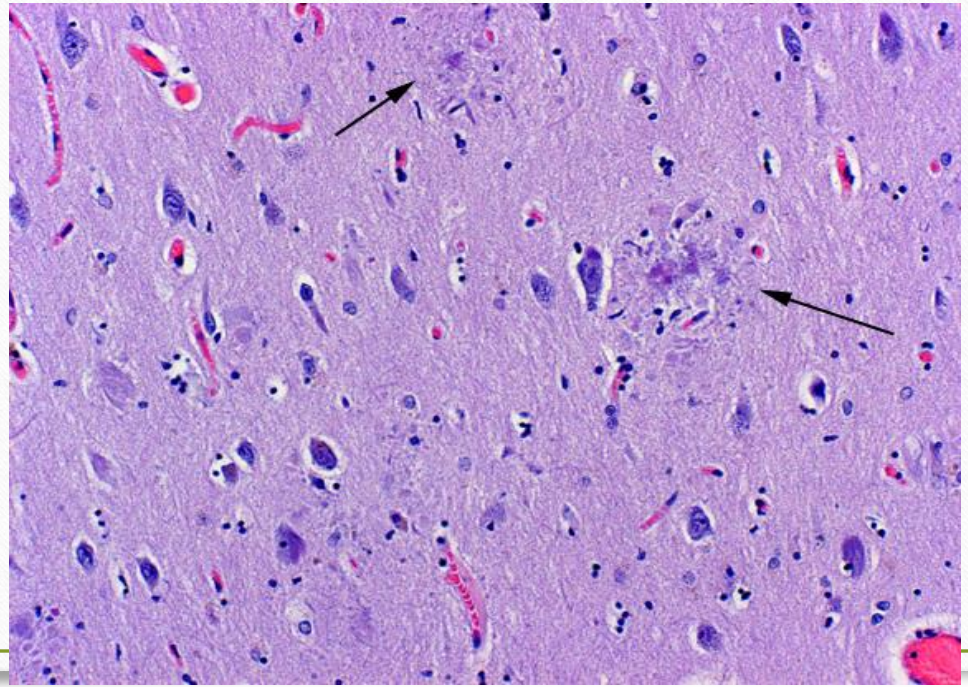


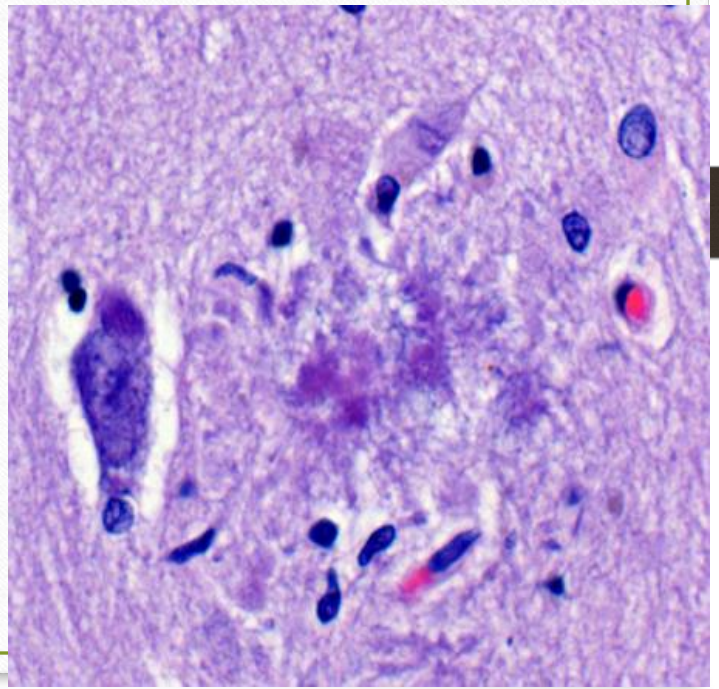


- Microscopy: Amyloid plaques (extracellular - accumulation of Aβ amyloid) and neurofibrillary tangles (intracellular - *Tau* accumulation).



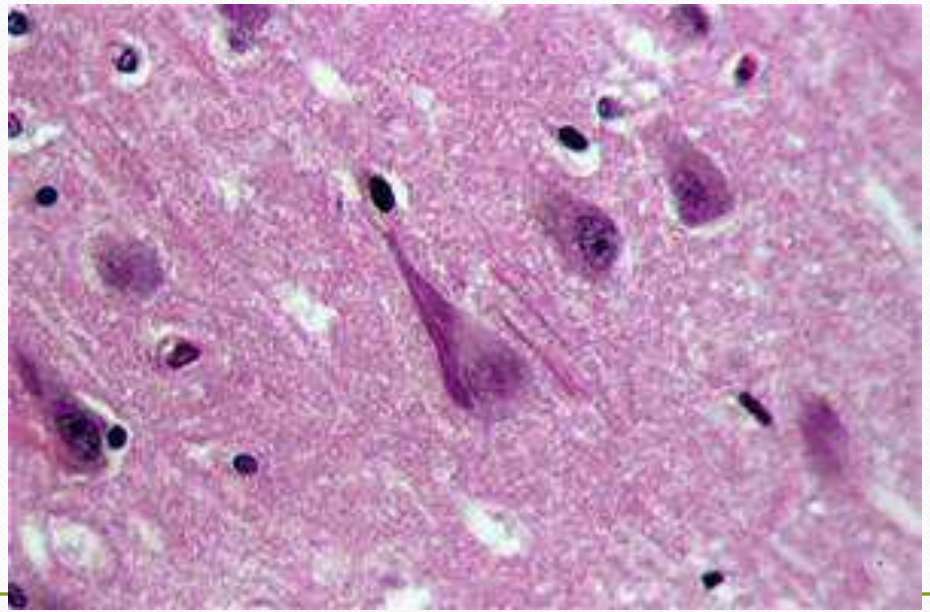
Neuritic plaques are focal, spherical collections of dilated, tortuous, processes of dystrophic neurites around a central amyloid (Aβ) core. Aβ deposition without neurites termed **diffuse plaques.**

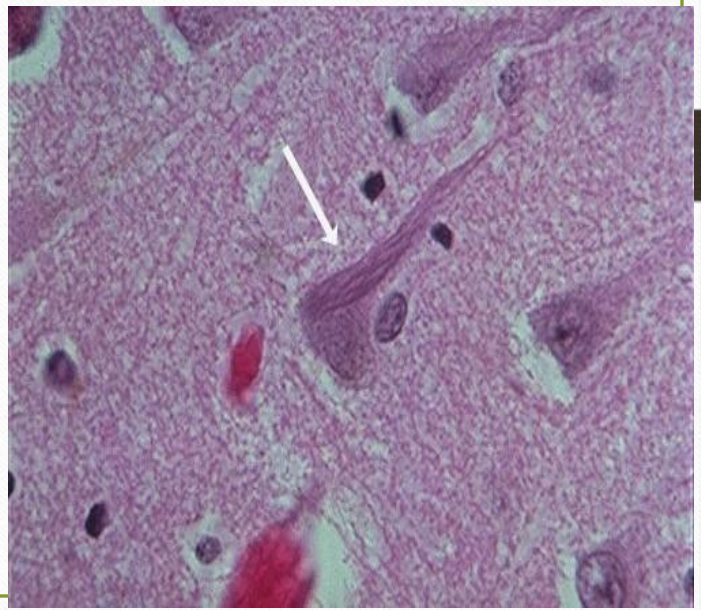




Neurofibrillary tangles: Tau containing bundles of filaments in neurons cytoplasm (encircle the nucleus), <**flame** shapes>

Where ? cortical neurons (entorhinal cortex), & the pyramidal cells of hippocampus, amygdala, basal forebrain, the raphe nuclei.

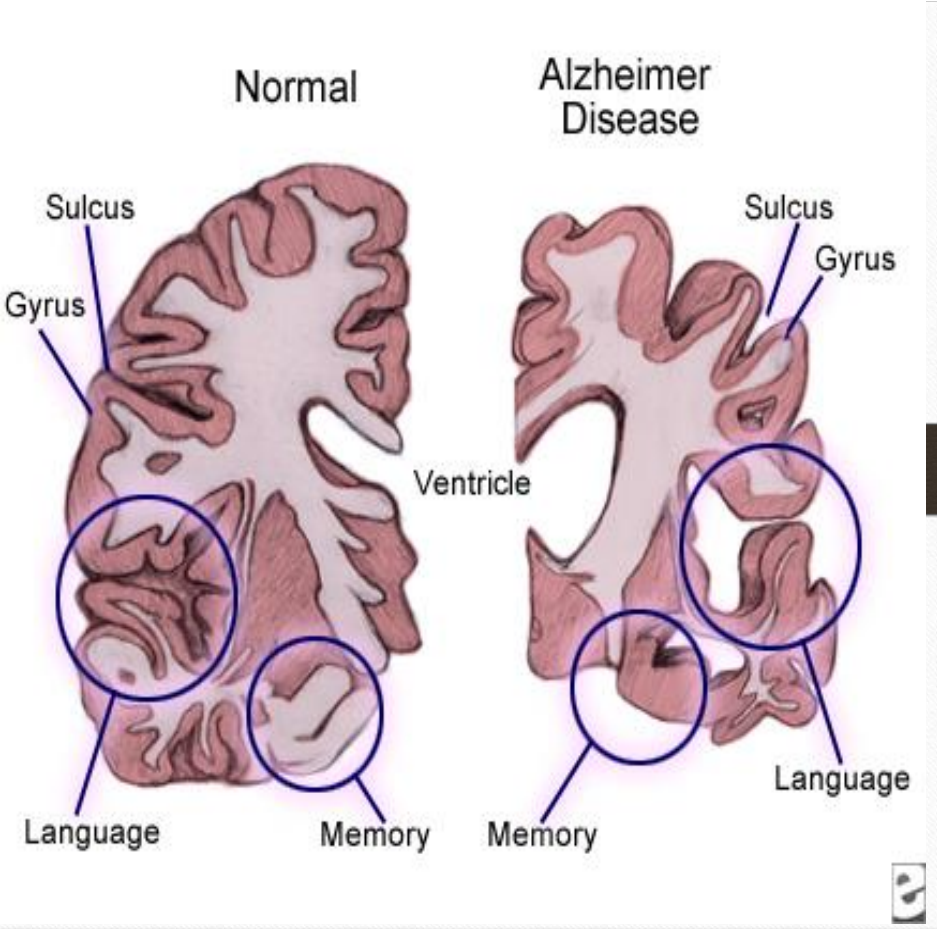




Clinically: Insidious onset of impaired higher intellectual function & memory, & altered mood & behavior.

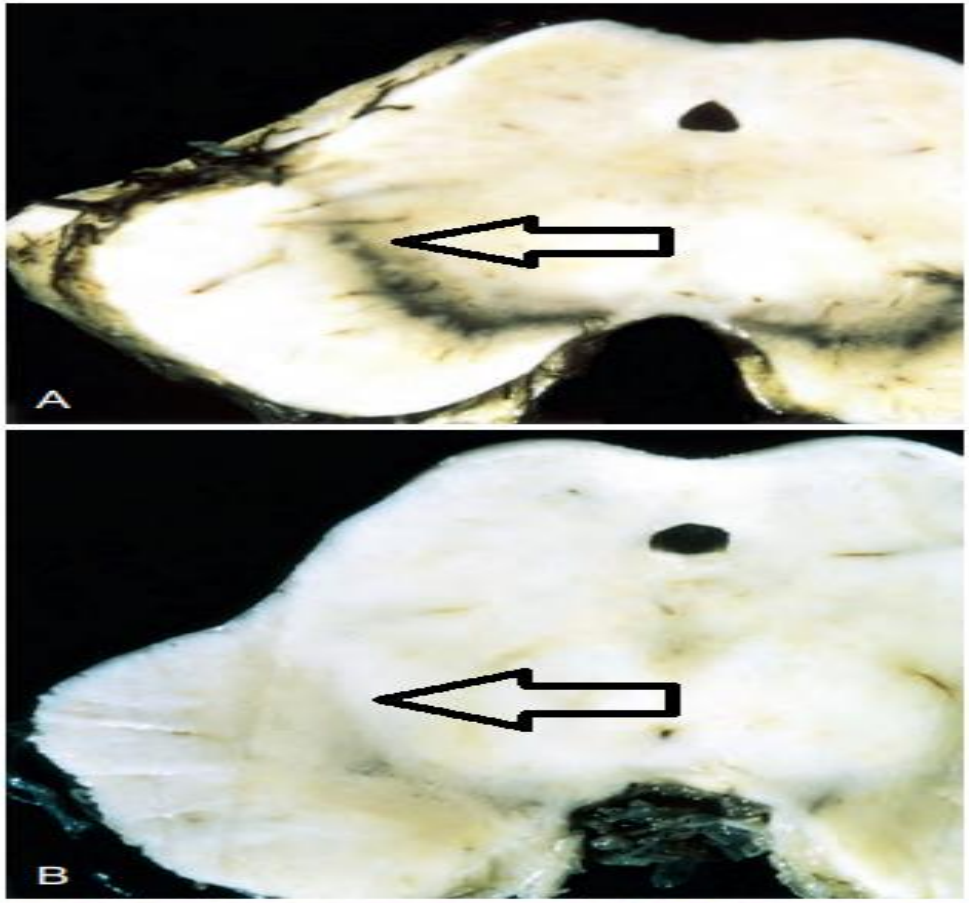
Over time, disorientation & aphasia. In final stages they are disabled, mute & immobile.

Death → intercurrent pneumonia or other infections.

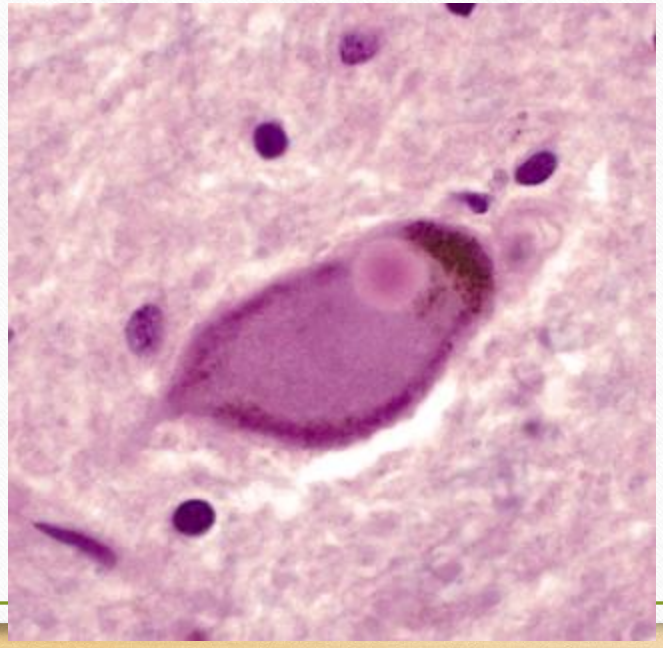


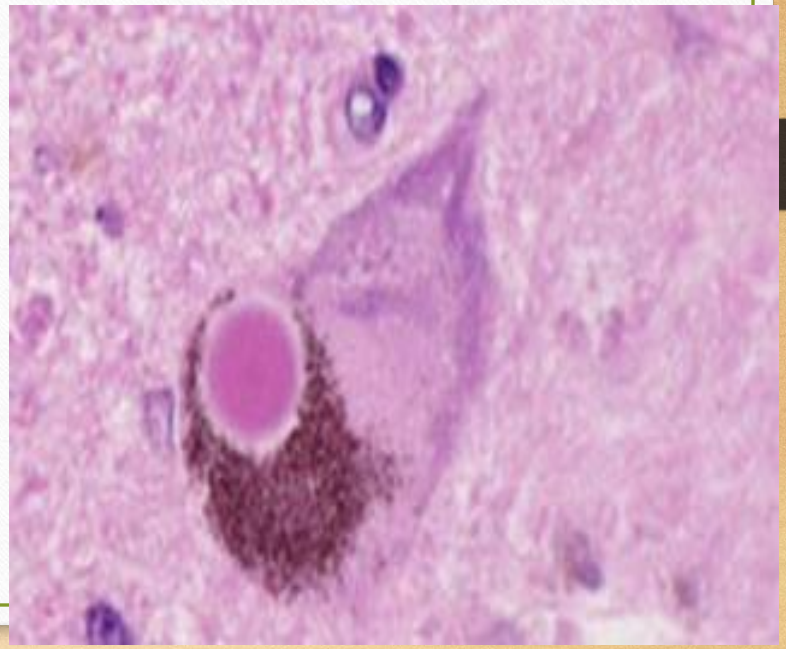
Parkinson Disease (PD)

At autopsy is pallor of the substantia nigra and locus ceruleus, due loss of pigmented catecholaminergic neurons.

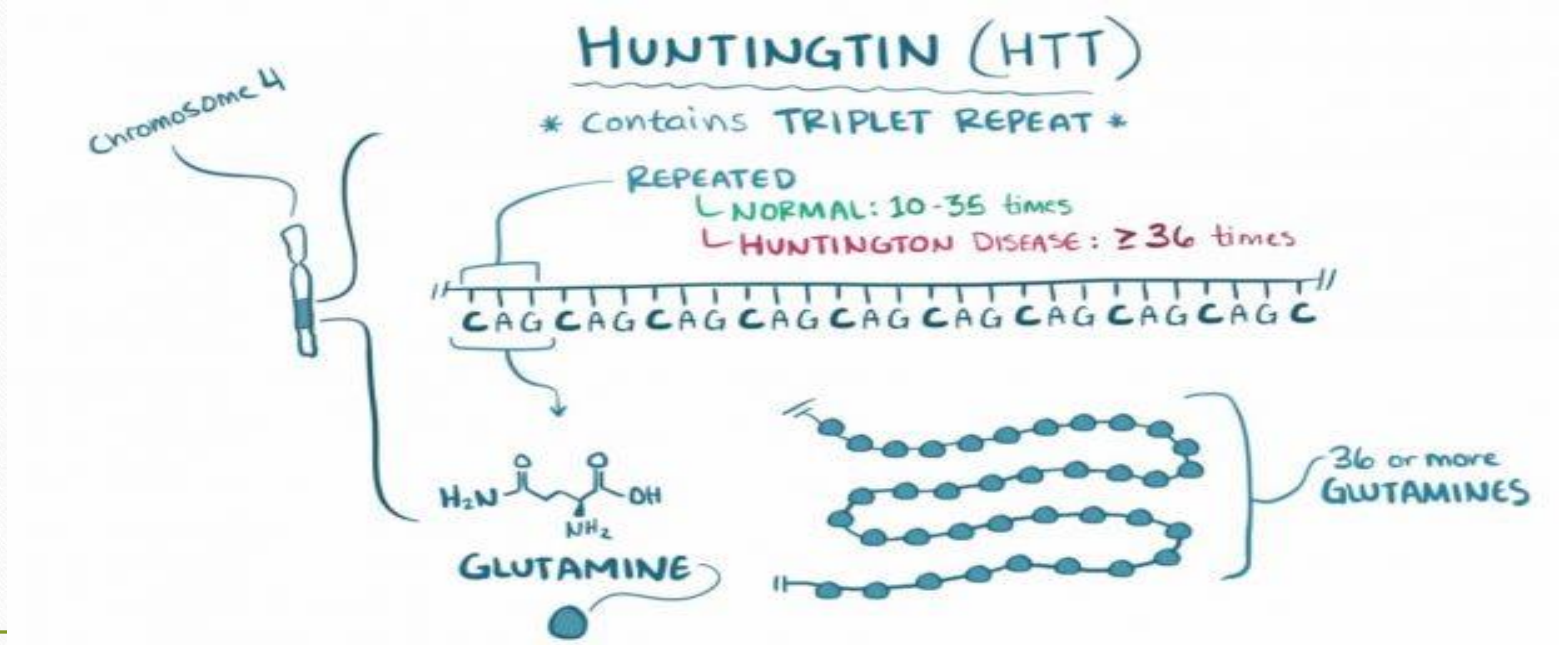


Areas of neuronal loss show gliosis. Lewy bodies found in those neurons that remain; single or multiple, cytoplasmic, eosinophilic, round inclusions (dense core with pale halo)





Huntington Disease (HD)



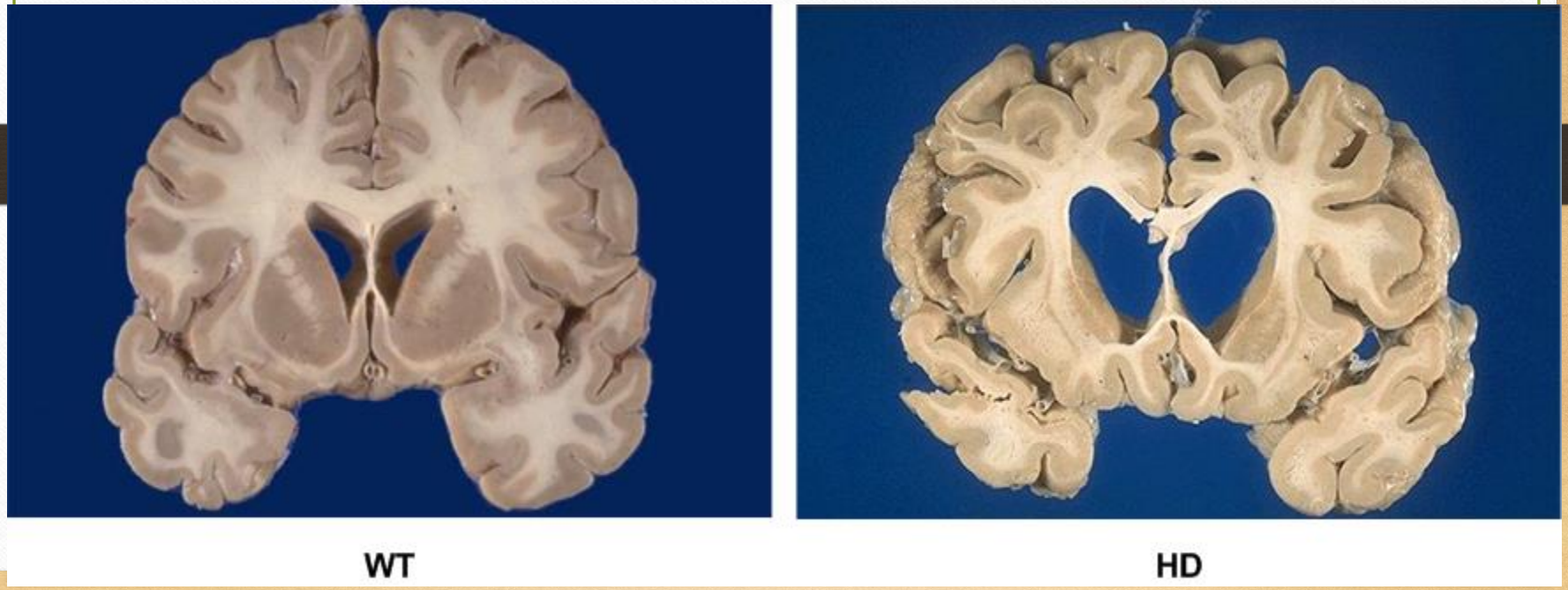
Huntington Disease-HD

- An autosomal **dominant** disease of progressive movement disorders & dementia caused by degeneration of the striatal neurons (caudate and putamen).
- Characterized by involuntary jerky movements (dystonic sometimes) of all parts of the body→ **Chorea.**
- Relentlessly progressive, resulting in death after an average 15 years.
- No sporadic form.

HD – Pathogenesis

- HD is caused by CAG **trinucleotide repeat expansions** in a gene on ch. 4, encodes the protein **Huntingtin**.
- Normal alleles contain 6 to 35 copies of the repeat; in HD the number of repeats is increased.
- A strong genotype-phenotype correlation → larger numbers of repeats resulting in earlier-onset disease. (average 40-50)
- Repeats occur during spermatogenesis → paternal transmission is associated with earlier onset in the next generation → **anticipation.**
- Mutant protein aggregates are potentially injurious.

The brain is small and shows striking atrophy of the caudate nucleus and, sometimes, the putamen. The lateral and third ventricles are dilated.



Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS)

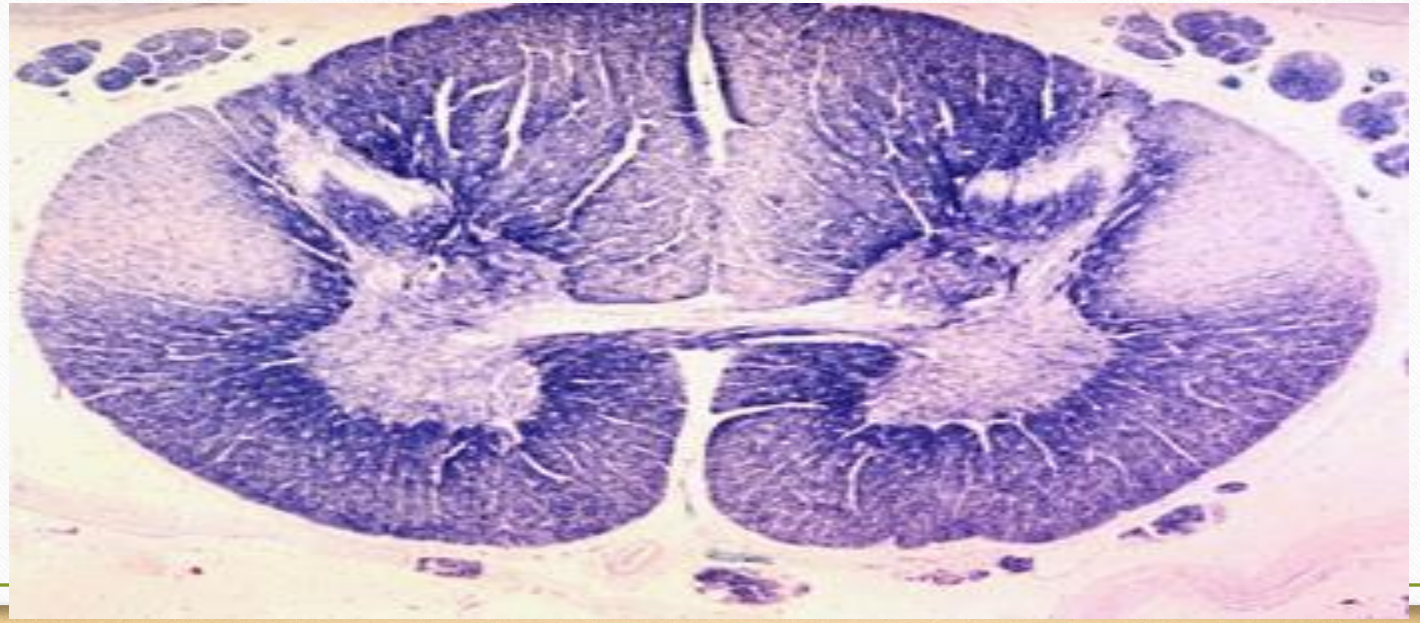
- The most common neurodegenerative disease affecting the motor system.
- A-Myo-trophic-lateral (corticospinal tracts –lateral column in spinal cord (SC))-sclerosis.
- A progressive disorder of loss of upper motor neurons in the cerebral cortex (Betz cells) and lower motor neurons in the SC and brainstem.
- Male slightly more than females, 5th decade & later.
- Sporadic 80% more common than familial.

ALS – pathogenesis

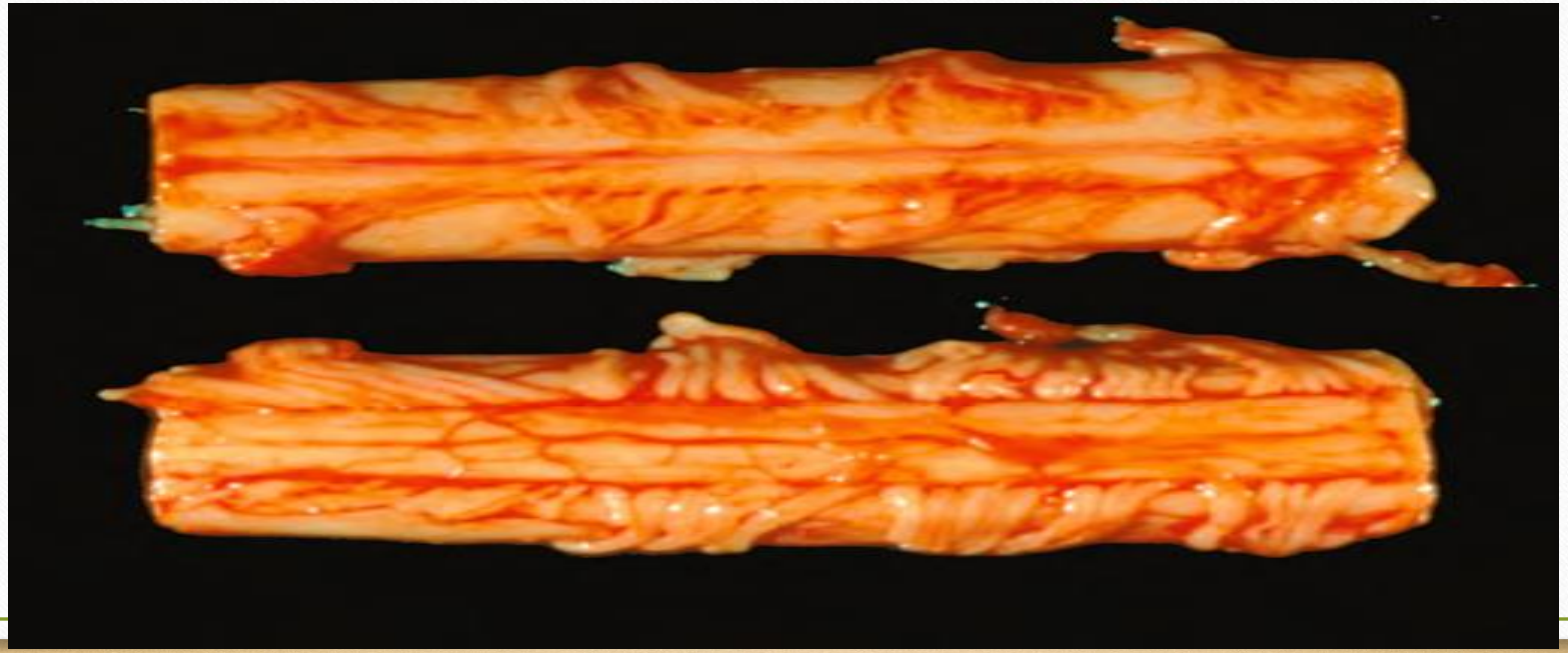
- Mutations in the superoxide dismutase gene, *SOD1*, on chr. 21 were the first identified genetic cause of ALS.
- Abnormal misfolded forms of the SOD1 protein are generated→ trigger 'unfolded protein response' in cells → apoptosis.

I. Death of **upper motor** neurons, causes degeneration of the descending corticospinal tracts.
II. Death of anterior horn cells (**lower motor** neurons) with loss of innervation causes atrophy of skeletal muscles.

Loss of the upper motor neurons leads to degeneration of the corticospinal tracts, resulting in volume loss and absence of myelinated fibers.



Segment of spinal cord viewed from anterior (upper) and posterior (lower) surfaces showing attenuation of anterior (motor) roots compared with posterior (sensory) roots.



ALS – Clinical

- Early symptoms include **asymmetric weakness of the hands** (dropping objects & difficulty performing fine motor tasks).
- Later, muscle strength & bulk diminish & involuntary contractions of individual motor units (**fasciculations**) occur.
- Eventual **respiratory muscles involvement** cause recurrent pulmonary infection, which is the usual cause of death.

Thiamine deficiency (Vitamine B1)

Wernicke encephalopathy

- Acute appearance of a combination of psychotic symptoms and ophthalmoplegia.
- Reversible when treated with thiamine.
- If this is unrecognized and untreated → irreversible syndrome → →

Korsakoff syndrome

- Disturbances of short term memory & confabulation.
- Common in chronic alcoholism.
- Also thiamine deficiency from gastric disorders (carcinoma, chronic gastritis, or persistent vomiting)

Wernicke encephalopathy is characterized by foci of hemorrhage and necrosis in the mamillary bodies and the walls of the third and fourth ventricles.